DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

November 24, 1999

WARNING LETTER
CHI-3-00

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Hymen T. Milgrom, President
Milex Products, Inc.
4311 North Normandy Ave
Chicago, IL 60634

Dear Mr. Milgrom:

An inspection was conducted of your medical device and pharmaceutical manufacturing facility from November 16, 1998 through January 20, 1999, by Investigators Yvonne Lozano, Bruce McCullough, and Norman Brown. The inspection covered the production of three pharmaceutical products manufactured by Milex: "Shur-Seal Contraceptive Gel," "Amino-Cerv Crème" and "Trimo-San Vaginal Jelly." These three products are drugs as defined by Section 201(g) of the Federal Food, Drug, and CosmeticAct (the Act). The inspection also covered the production of several obstetric products manufactured by Milex. These products are devices as defined by Section 201(h) of the Act.

The inspection covering the production of the aforementioned drug products revealed significant deviations from Current Good Manufacturing Practice Regulations (CGMP), Title 21, Code of Federal Regulations, Part 211. These CGMP deficiencies cause these drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Act. The deviations reported included:

> Failure to withhold each lot of components, containers, and closures from use until the lot has been sampled, tested, and examined for conformity with all appropriate written specifications for purity, strength, and quality [21 CFR 211.82(b) and 211.84(a)].
>
> Failure to establish and follow laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that in-process materials and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(a) and (b)].

Failure to establish and follow adequate written procedures for production and process controls covering all aspects of the firm's operations designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a) and (b)].

Failure to establish and follow procedures designed to prevent objectionable microorganisms in drug products not required to be sterile [21 CFR 211.113(a)].

Failure of the Quality Control Unit to review and approve all drug product production and control records to determine compliance with all procedures before a batch is released [21 CFR 211.192].

Failure to establish and follow written procedures which identify the responsibilities and procedures applicable to the Quality Control Unit [21 CFR 211.22].

Failures of batch production and control records to include complete information relating to the production and control of each batch [21 CFR 211.188].

Failure to maintain a complete record of all data generated during testing, including all graphs, charts and spectra from laboratory instrumentation [21 CFR 211.194].

Failure to establish and follow written procedures which identify the responsibilities and procedures applicable to the quality control unit [21 CFR 211.22].

Failure to establish and follow written procedures which describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch [21 CR 211.110].

Failure to establish and follow written procedures which require evaluation, at least annually, of the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures [21 CFR 211.180(e)(1)].

Following the inspection, the labeling for Trimo-San Vaginal Jelly was reviewed. The label for this product states that it contains as the active ingredients oxyquinoline sulfate, 0.025%, and sodium lauryl sulfate, 0.01%, adjusted with triethanolamine to pH 4. The labeling for Trimo-San Vaginal Jelly states that it is "A Unique Vaginal Product," and that the "Purpose of TRIMO-SAN" is:

1. To help restore and maintain normal vaginal acidity.
2. To coat walls of vagina with a lubricating film that controls odor-causing bacteria.
3. To combat on contact, annoying vaginal symptom such as itching and soreness.
4. To provide prompt symptomatic relief of minor vaginal irritations.
5. To promote comfort in pessary wearers.
6. To help prevent vaginal or cervical erosion.
7. To help prevent pressure necrosis.

Trimo-San Vaginal Jelly is labeled for use three times daily during the first week of treatment and two times a week thereafter. The labeling does not include any time limit when the product should be used.

Based on the intended uses cited above, this product is a drug within Section 201(g) of the Act. We do not have any information which shows that your product or similarly formulated and labeled OTC products were marketed as OTC drugs in the United States before December 4, 1975. We do not know of any substantial scientific evidence that demonstrates that this product is generally recognized as safe and effective for its intended uses.

Trimo-San Vaginal is a new drug [Section 201(p) of the Act] which may not legally be marketed in this country without an approved new drug application [Section 505(a) of the Act]. This product is also misbranded [Section 502(f)(1) of the Act] in that its labeling fails to bear adequate directions for use.

The above CGMP violations, as well as other significant violations covering both medical device and drug manufacturing, were listed on the Form FDA 483, List of Observations, which was issued and discussed with you at the conclusion of the inspection. It is your responsibility to ensure that all of your drug and device products are in compliance with federal law and regulations. Failure to promptly correct these violations may result in regulatory action without further notice. Such action includes seizure and/or injunction. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your response to the Form FDA 483, dated March 18, 1999. In some instances, you disputed the existence of deficiencies that were listed on the Form FDA 483. For example, you questioned item #55 of the FDA 483 saying that you were unaware that each batch record is required to be reviewed annually. Section 211.180(e)(1) requires that a "representative number of batches" be reviewed periodically for quality standards. The word "representative" was inserted into this regulation in January 1995, to confirm that every batch does not necessarily have to be included. Every drug product must have at least one batch included in the annual review. Reviewing batches that exhibit varying manufacturing experiences is a critical element ensuring

that a "representative" selection is made. Batches showing different categories of experiences would include those that have been approved, rejected and recalled; have unexplained discrepancies; or have any kind of outcome that may indicate changes are needed.

You also requested clarification on item #30 of the FDA 483 which cited Milex for "Failure to have procedures in place for microbial control. No testing is performed and there are no written specifications for microbial activity." Both Amino-Cerv Crème and Trimo-San Vaginal Jelly are multi-dose units and therefore especially susceptible to microbial contamination. Amino-Cerv Crème is specifically indicated for use after cervical tears. Pathogenic objectionable organisms generally grow at body temperature and can be intrusive in the body through open wounds. All three of these formulations contain Methyl Paraben NF, an anti-microbial preservative, however, no testing has been conducted to prove that the formulation contains Methyl-Paraben NF at levels that are effective in preventing microbial growth. All three of your firm's products have water as their largest component, however, Milex does not use Purified Water, USP. Rather, your firm uses city tap water with a 5 micron debris filter. This size filter is not small enough to control the microbial load. Also, there is no filter in the water system small enough to control the microbial load. Title 21, CFR, Part 211.113(a), discussed above, addresses this requirement.

In some instances, you indicated that Milex has initiated a number of corrective actions in response to the investigator's findings. You also provided estimated completion dates for these changes. You may reference your earlier response in your response to this Warning Letter. Please discuss the status of the corrective actions you indicated Milex was taking in your response. We will need to assess the adequacy of these promised corrections during an inspection of your facility.

Please notify this office in writing within 30 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent recurrence of similar violations. If corrective action cannot be completed within 30 days, state the reason for the delay and the time frame within which the corrections will be completed.

Your reply should be sent to George F. Bailey, Compliance Officer.

Sincerely,

\s\
Raymond V. Mlecko
District Director